

Please replace paragraph [0013] starting on Page 4 with the following:

[0013] wherein

Ar¹ is an aromatic or heteroaromatic group;

R¹, R², R³, R⁴ and R⁵ which may be the same or different is each an atom or group -L²(Alk³)_tL³(R⁷)_u in which L² and L³ which may be the same or different is each a covalent bond or a linker atom or group,

t is zero or the integer 1,

u is an integer 1, 2 or 3,

Alk³ is an aliphatic or heteroaliphatic chain and R⁷ is a hydrogen or halogen atom or a group selected from alkyl, -OR⁸, where R⁸ is a hydrogen atom or an optionally substituted alkyl group, -SR⁸, -NR⁸R⁹, where R⁹ is as just defined for R⁸ and may be the same or different, -NO₂, -CN, -CO₂R⁸, -SO₃H, -SOR⁸, -SO₂R⁸ -OCO₂R⁸, -CONR⁸R⁹, -OCONR⁸R⁹, -CSNR⁸R⁹, -COR⁸, -OCOR⁸, -N(R⁸)COR⁹, -N(R⁸)CSR⁹, -SO₂N(R⁸)(R⁹), -N(R⁸)SO₂R⁹, -N(R⁸)CON(R⁹)(R¹⁰), where R¹⁰ is a hydrogen atom or an optionally substituted alkyl group, -N(R⁸)CSN(R⁹)(R¹⁰) or -N(R⁸)SO₂N(R⁹)(R¹⁰);

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a covalent bond or a linker atom or group;

Alk² is a straight or branched alkylene chain;

m is zero or an integer 1;

R⁶ is a hydrogen atom or a methyl group;

r is zero or the integer 1;

R is a carboxylic acid (-CO₂H) or a derivative thereof;

R^a is a hydrogen atom or a methyl group;

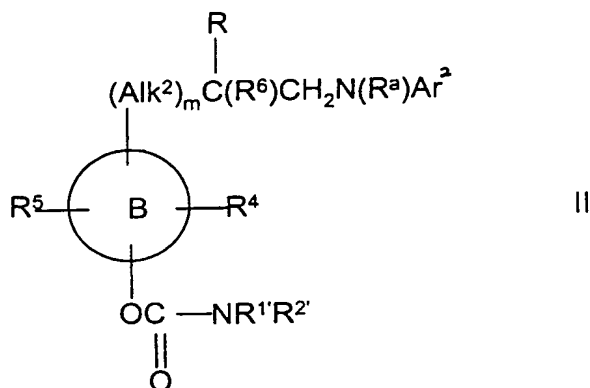
Ar² is an optionally substituted aromatic or heteroaromatic group;

B is a nitrogen containing heteroaryl group;

and the salts, solvates, hydrates and N-Oxides thereof.

Please replace paragraph [0014] starting on Page 5 with the following:

[0014] Another class of compounds within the scope of this invention include compounds of formula (II)



Please replace paragraph [0015] on Page 6:

A⁴

[0015] wherein R, R^a, R⁴, R⁵, R⁶, Alk², B, m and Ar are as defined above and R^{1'} and R^{2'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, heteroaryl or and R^{1'} and R^{2'}, together with the nitrogen atom to which they are attached, are joined to form an optionally substituted heterocyclic ring; and the salts, solvates, hydrates and N-oxides thereof.

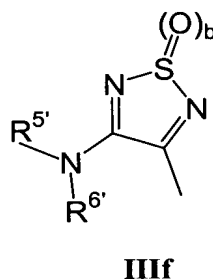
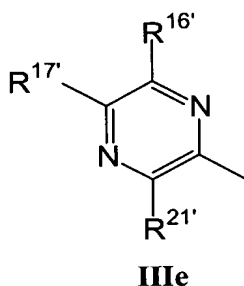
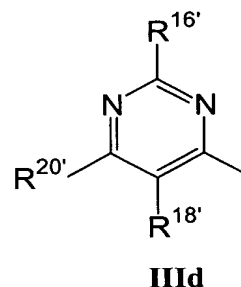
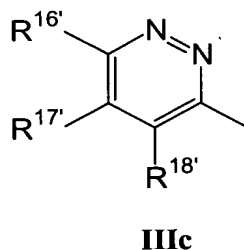
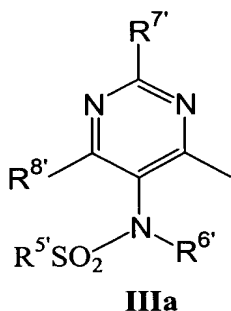
Please replace paragraph [0016] on Page 6 with the following:

A⁵

[0016] In one preferred embodiment, and R^{1'} and R^{2'} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, or and R^{1'} and R^{2'}, together with the nitrogen atom to which they are attached, are joined to form an optionally substituted heterocyclic ring provided that said substituted alkyl, substituted alkenyl and substituted cycloalkyl do not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group.

Please replace paragraph [0017] starting on Page 6 with the following:

Preferably, in the compounds of this invention, Ar² is selected from the group consisting of moieties of formula IIIa, IIIc, IIIe or IIIf:



Please replace paragraph [0027] on Page 9 with the following:

A7

[0027] It will be appreciated that compounds of formula (1) may have one or more chiral centers, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and (II) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

Please replace paragraph [0032] starting on Page 10 with the following:

A8

[0032] Particular examples of aliphatic chains represented by Alk¹ include optionally substituted -CH₂-, -CH₂CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -(CH₂)₂CH₂-,

A8
cont-

-CH(CH₃)CH₂-, -(CH₂)₃CH₂-, -CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂CH₂-,
-(CH₂)₄CH₂-, -(CH₂)₅CH₂-, -CHCH-, -CHCHCH₂-, -CH₂CHCH-, -CHCHCH₂CH₂-,
-CH₂CHCHCH₂-, -(CH₂)₂CHCH-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-,
-CH₂CCCH₂-, or -(CH₂)₂CC- chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L⁴ to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted -L⁴CH₂-, -CH₂L⁴CH₂-, -L⁴(CH₂)₂-, -CH₂L⁴(CH₂)₂-, (CH₂)₂L⁴CH₂-, -L⁴(CH₂)₃- and -(CH₂)₂L⁴(CH₂)₂- chains. The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk¹ include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₆ alkoxy, e.g. methoxy or ethoxy, thiol, C₁₋₆ alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR¹² and -N(R¹²)₂ groups where R¹² is an optionally substituted straight or branched alkyl group as defined below for R¹¹. Where two R¹² groups are present these may be the same or different. Particular examples of substituted chains represented by Alk¹ include those-specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type -CH(CF₃)-, -C(CF₃)₂-, -CH₂CH(CF₃)-, -CH₂C(CF₃)₂-, -CH(CF₃)- and -C(CF₃)₂CH₂.

Please replace paragraph [0034] starting on Page 11 with the following:

A9

[0034] When in the compounds of formula (1) L¹, L² and/or L³ is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R¹¹)-, where R¹¹ is a hydrogen atom or an optionally substituted alkyl group, -CON(R¹¹)-, -OC(O)N(R¹¹)-, -CSN(R¹¹)-, -N(R¹¹)CO-, -N(R¹¹)C(O)O-, -N(R¹¹)CS-, -S(O)₂N(R¹¹)-, -N(R¹¹)S(O)₂-, -N(R¹¹)CON(R¹¹)-, -N(R¹¹)CSN(R¹¹)-, or -N(R¹¹)SO₂N(R¹¹)- groups. Where the linker group contains two R¹¹ substituents, these may be the same or different.

✓
Please replace paragraph [0042] starting on Page 15 with the following:

[0042] Optional substituents which may be present on the aromatic or heteroaromatic groups represented by Ar² include one, two, three or more substituents, each selected from an atom or group R¹³ in which R¹³ is -R^{13a} or -Alk⁴ (R^{13a})_m,

A10
wherein R^{13a} is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl (-C(=O)OH), esterified carboxyl, thiol (-SH), substituted thiol, -COR¹⁴, -CSR¹⁴, -SO₃H, -SO₂R¹⁴, -SO₂NH₂, -SO₂NHR¹⁴, -SO₂N(R¹⁴)₂, -CONH₂, -CSNH₂, -CONHR¹⁴, -CSNHR¹⁴, -CON(R¹⁴)₂, -CSN(R¹⁴)₂, -N(R¹²)SO₂R¹⁴, -N(SO₂R¹⁴)₂, -NH²(R¹¹)SO₂NH₂, -N(R¹¹)SO₂NHR¹⁴, -N(R¹¹)SO₂N(R¹⁴)₂, -N(R¹¹)COR¹⁴, -N(R¹¹)CON(R¹⁴)₂, -N(R¹¹)CSN(R¹⁴)₂, -N(R¹¹)CSR¹⁴, -N(R¹¹)C(O)OR¹⁴, -SO₂NHet¹, -CONHet¹, -CSNHet¹, -N(R¹¹)SO₂NHet¹, -N(R¹¹)CONHet¹, -N(R¹¹)CSNHet¹, -Het², -SO₂N(R¹¹)Het², -CON(R¹¹)Het², -CSN(R¹¹)Het², -N(R¹¹)CON(R¹¹)Het², -N(R¹¹)CSN(R¹¹)Het², aryl or heteroaryl group;

wherein

R¹⁴ is an aryl or heteroaryl group,

-NHet¹ is an optionally substituted C₅₋₇cyclicamino group optionally containing one or more other -O- or -S- atoms or -N(R¹¹)-, -C(O)- or -C(S)-groups,

Het² is an optionally substituted monocyclic C₅₋₇carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R¹¹)-, -C(O)- or -C(S)-groups,

Alk⁴ is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_n, where n is an integer 1 or 2, or -N(R¹⁵)- groups, where R¹⁵ is a hydrogen atom or C₁₋₆alkyl, e.g. methyl or ethyl group; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R¹¹ or R¹⁴ groups are present in one of the above substituents, the R¹¹ or R¹⁴ groups may be the same or different.

Please replace paragraph [0047] starting on Page 16 with the following:

A11 [0047] Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^5$ wherein Alk^5 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^5 group include R^{13a} substituents described above.

Please replace paragraph [0051] starting on Page 18 with the following:

A12 [0051] Particularly useful atoms or groups which can be substituents on Ar^2 include fluorine, chlorine, bromine or iodine atoms, or C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, or thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, C_{1-6} alkylamino, e.g. methylamino or ethylamino, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxy C_{1-6} alkyl, e.g. carboxyethyl, C_{1-6} alkylthio e.g. methylthio or ethylthio, carboxy C_{1-6} alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxy-propylthio, C_{1-6} alkoxy, e.g. methoxy or ethoxy, hydroxy C_{1-6} alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{5-7} cycloalkoxy, e.g. cyclopentyloxy, halo C_{1-6} alkyl, e.g. trifluoromethyl, halo C_{1-6} alkoxy, e.g. trifluoromethoxy, C_{1-6} alkylamino, e.g. methylamino or ethylamino or propylamino, optionally substituted C_{6-12} aryl C_{1-6} alkylamino, e.g. benzylamino, fluorobenzylamino or hydroxyphenylethylamino, amino ($-NH_2$), amino

A12
cont.

C₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, aminoC₁₋₆alkylamino e.g. aminomethylamino, aminoethylamino or aminopropylamino, Het¹NC₁₋₆alkylamino e.g. morpholinopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino, e.g. hydroxyethylamino, hydroxypropylamino or hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, vitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁵, where Alk⁵ is as defined above, C₁₋₆alkanoyl e.g. acetyl, propyl or butyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. Thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), C₁₋₆alkyl-sulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl, propylsulphonyl, hexylsulphonyl or isobutylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylamino-sulphonyl or diethylaminosulphonyl, optionally substituted phenylamino-sulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl, diethylaminocarbonyl or dipropylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. Aminoethylaminocarbonyl, C₁₋₆ dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonyl-amino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino,

A12
cont.

C₁₋₆alkyl-aminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆ dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonyl-amino or diethylaminosulphonylamino, optionally substituted morpholine-sulphonylamino or morpholinesulphonylC₁₋₆alkyl-amino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. Acetylamino, aminoC₁₋₆alkanoylamino e.g. Aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. Acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. Acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxy carbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Please delete paragraph [0058] starting on Page 21.

Please replace paragraph [0067] starting on Page 23 with the following:

A13

[0067] In compounds of formulae (1) and (2) m is preferably 1 and Alk² is preferably -CH₂-.

Please replace [✓]paragraph [0072] starting on Page 24 with the following:

A14

[0072] Other atoms or groups which can be substituents on Ar² include a halogen atom, especially fluorine or chlorine, morpholinyl, thiomorpholinyl, optionally substituted

A14
cont.
piperidinyl, especially piperidinyl or 4-carboxypiperidinyl, pyrrolidinyl, optionally substituted piperazinyl, especially t-butyloxycarbonylpiperazinyl, thioC₁₋₆alkyl, especially thiomethyl, thioethyl or thiopropyl, optionally substituted thiobenzyl, especially thiobenzyl, haloC₁₋₆alkyl, especially trifluoromethyl, C₁₋₆alkyloxy, especially methoxy, ethoxy or propoxy, optionally substituted benzyloxy, especially benzyloxy, haloC₁₋₆alkoxy, especially trifluoromethoxy and difluoromethoxy, C₁₋₆alkylamino, especially methylamino, ethylamino or propylamino, C₁₋₆dialkylamino, especially dimethylamino or diethylamino, optionally substituted C₆₋₁₂arylC₁₋₆alkylamino, especially benzylamino, 4-substituted benzyl, especially 4-fluorobenzylamino or 4-hydroxyphenylethylamino, aminoalkylamino, especially 3-aminopropylamino, Het¹ NC₁₋₆alkylamino, especially 3-morpholinopropylamino, optionally substituted phenoxy, especially phenoxy, hydroxyC₁₋₆alkylamino, especially 2-hydroxyethylamino, 3-hydroxypropylamino and 3-hydroxybutylamino, nitro, carboxyl, -CO₂Alk⁵, where R⁵ is as defined above, especially carboxymethyl and carboxyethyl, carboxamido, C₁₋₆alkylaminocarbonyl, especially methylaminocarbonyl, ethylaminocarbonyl and propylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, especially dimethylaminocarbonyl, diethylaminocarbonyl or dipropylaminocarbonyl, C₁₋₆alkanoyl, especially acetyl, propyl or butyryl, optionally substituted benzoyl, especially benzoyl, C₁₋₆alkylsulphinyl, especially methylsulphinyl, ethylsulphinyl or propylsulphinyl, C₁₋₆alkylsulphonyl, especially methylsulphonyl, ethylsulphonyl, propylsulphonyl, hexylsulphonyl or isobutylsulphonyl, C₁₋₆alkylaminosulphonyl, especially ethylaminosulphonyl or propylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, especially diethylaminosulphonyl, C₁₋₆alkylaminocarbonyl, especially methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, especially dimethylaminocarbonyl or diethylaminocarbonyl.

Please replace paragraph [0159] starting on Page 56 with the following:

A15
[0159] In a further example compounds of formula (4) [R^a, R^b are H,] can be converted into compounds of formula (5) by treatment with nitrous acid, or isoamyl nitrite